Aquaporins

An Introduction to a Key Factor in the Mechanism of Skin Hydration

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Abstract

While it is well known that a balanced level of hydration is fundamental for healthy skin, the physiological mechanisms underlying the control of hydration, particularly in the epidermis, are yet to be fully elucidated. Over the past 10 years, much research has been carried out to understand the nature and regulation of the water gradient that exists across the layers of the epidermis. Of central importance is the role played by membrane-bound pores called aquaporins, which facilitate the passage of water and, in some cases, small molecules such as glycerol. This paper provides an overview of the principal aquaporin present in the epidermis, aquaporin 3, and how the level of hydration of the epidermis is correlated to endogenous levels of glycerol and to the distribution of aquaporin 3 channels. The role of aquaporin 3 in skin diseases is considered along with possible clinical implications of aquaporin 3 modulation.

Introduction

The skin is a critical protective organ of the body, shielding the internal tissues from external mechanical, chemical, thermal, microbial, and radiation exposures, and also acts as a barrier to water and heat loss. The epidermis, a homeostatic and self-renewing tissue, requires a balanced level of hydration for the ideal proliferation, differentiation, and physiological integrity of the epithelial cells of which it is composed. Water is vital for the proper physiological functioning and maintenance of the epidermis, and for the outward appearance of healthy skin. Both overhydration and underhydration can lead to alterations in the mechanical properties of skin, causing skin breakdown and tissue maceration due to increased permeability (e.g., resulting from wound repair, bacterial/fungal colonization) in the case of the former or dry and visibly altered appearance in the case of the latter.[1,2]

Despite the ubiquitous presence of water throughout the body, little is known about the mechanisms underlying skin hydration. Investigations into hydration have focused predominantly on diseased skin. Consequently, the underlying mechanism for maintaining a balance between water retention and water loss in normal skin is not fully understood. Studies have shown that the level of skin hydration is dependent on several factors, including 1) the presence of natural hygroscopic agents called natural moisturizing factors within the corneocytes, 2) the presence of endogenous glycerol as a natural humectant and of hyaluronic acid in the epidermis and dermis, 3) the ordered lamellar arrangement of intercellular lipids in the stratum corneum (SC) that form a barrier to transepidermal water loss, and 4) the presence of tight junctions within the stratum granulosum to further impede water loss.[3,4] However, while these components function in concert to maintain water levels and limit water loss, they do not reveal how water gets into the epidermis in the first place.

Aquaporins Facilitate the Movement of Water and Other Small Molecules

It was previously assumed that biological membranes were freely permeable to water. However, more recent studies have shown that membranes from certain tissue types exhibit altered biophysical properties with respect to water transport, resulting in differences in water permeability in different tissues. Observations, such as temperature-dependent water transport and heightened osmotic versus diffusional permeability, led to the idea that water may move through pore-like channels.[5]

In 1992, the research group led by

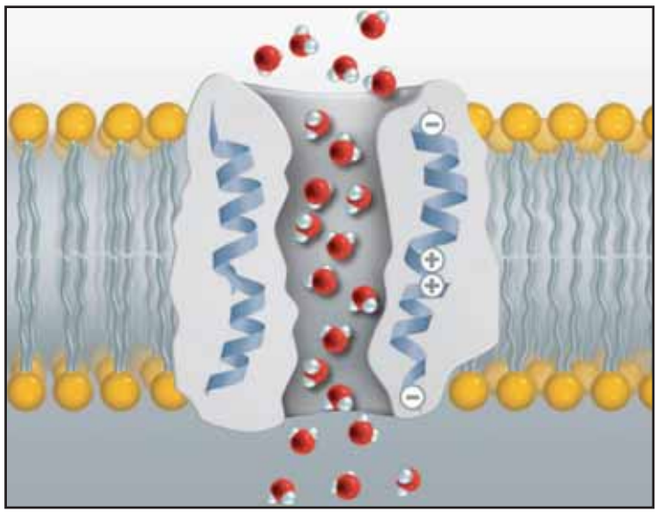

Figure 1. Aquaporin 3 channel. Schematic representation of the structure of a cell membrane-bound aquaporin channel. Aquaporins are made up of six transmembrane α-helices arranged in a right-handed bundle. The width of the pore at its narrowest point, together with charged residues on the α-helices, allows only the diffusion through the channel of small, uncharged molecules such as water and glycerol along osmotic or concentration gradients.

Peter Agre reported the discovery of the first of a family of cell membrane-bound water channels called aquaporins (AQPs), for which he was jointly awarded the Nobel Prize in Chemistry in 2003.[6–8] These channels are highly conserved throughout evolution, having been identified in plants, insects, amphibians, and mammals, and play an essential role in cellular water homeostasis.[9] AQPs increase the permeability of cell membranes to the bidirectional, osmotically driven passage of small uncharged molecules, such as water, glycerol, and urea (Figure 1).

Aquaporin 3 and Its Role in Skin

In mammals, 13 AQPs have been identified that differ with respect to transport capabilities, tissue allocation, and function.[10,11] Some AQPs are directly involved in water transport,[12] while others transport water, glycerol, and other small solutes, such as urea.[3,10] The most abundant AQP present in the skin—and more specifically in the plasma membrane of epidermal keratinocytes[9]—is aquaporin 3 (AQP3). AQP3 is in fact an aquaglyceroporin, meaning that it transports both water and glycerol.

The importance of the role of AQP3 in the skin has been elucidated by investigations on genetically modified AQP3 knock-out mice.[13] Mice lacking AQP3 manifest reduced SC hydration that cannot be corrected by skin occlusion or exposure to a high-humidity environment. Analysis of these mice revealed a reduced glycerol content of the SC and epidermis compared with control animals, with both types showing normal glycerol content in the dermis and serum. No other differences were observed with respect to the SC structure, lipid profile, protein content, or concentrations of amino acids, ions, and other small solutes.[14] These results suggested an important role for AQP3-facilitated glycerol transport in regulating SC and epidermal glycerol content and showed that glycerol content is a key determinant of skin hydration at the different levels of the epidermis.[14]

Glycerol acts as an endogenous humectant that diffuses osmotically into the SC and underlying epidermis, pulling water with it and creating a reservoir effect, thereby enhancing the water-holding capacity of the skin (Figure 2). Glycerol thus plays an important role in hydration of the skin, in providing cutaneous elasticity, and in facilitating epidermal barrier repair.[15] Besides its humectant function, glycerol has a number of additional effects in the skin, including influencing lipid composition and metabolism in the SC, which in turn influence barrier function.[15] Endogenous glycerol, a product of the breakdown of triglycerides, appears to have two main sources in the body—the serum, into which both glycerol and fatty acids are released after triglyceride hydrolysis, and the sebaceous glands, which exhibit high levels of triglyceride turnover.[16] Several investigators have proposed that the primary source of the glycerol transported by AQP3 is from the serum.[14,16,17]

From a physiological perspective, the maintenance of hydration can be achieved by both endogenous and exogenous glycerol. It has been shown that glycerol, but not glycerol analogs, administered by topical or systemic (intraperitoneal and oral) routes corrected the reduced hydration in AQP3-null mice to levels similar to those seen in the wild-type mice.[18]

Importantly, the endogenous levels of glycerol have been shown to be correlated with the level of SC hydration[16,19] as determined by glycerol content analysis of tape-stripped skin and corneometer measurement of SC hydration. In addition, immunohistochemical analysis of AQP3 expression shows that the distribution of AQP3 reflects the epidermal water allocation and water gradient throughout the epidermis, and that membrane water permeability is high, confirming that AQP3 is functional.[4,9] In the healthy epidermis, AQP3 is mainly found in the stratum basale, with decreasing expression toward the stratum granulosum.[4] The AQP3 gradient parallels a corresponding water gradient in the epidermis with a sharp decrease of water content in the SC (10–15% water content),[9] compared with the underlying layers (75%).[4] This ensures that the viable layers of the epidermis are optimally hydrated while water loss is minimized.[20] Thus, it appears that AQP3-mediated diffusion of glycerol—and by implication, of water—is a fundamental mechanism for hydration of skin.[14]

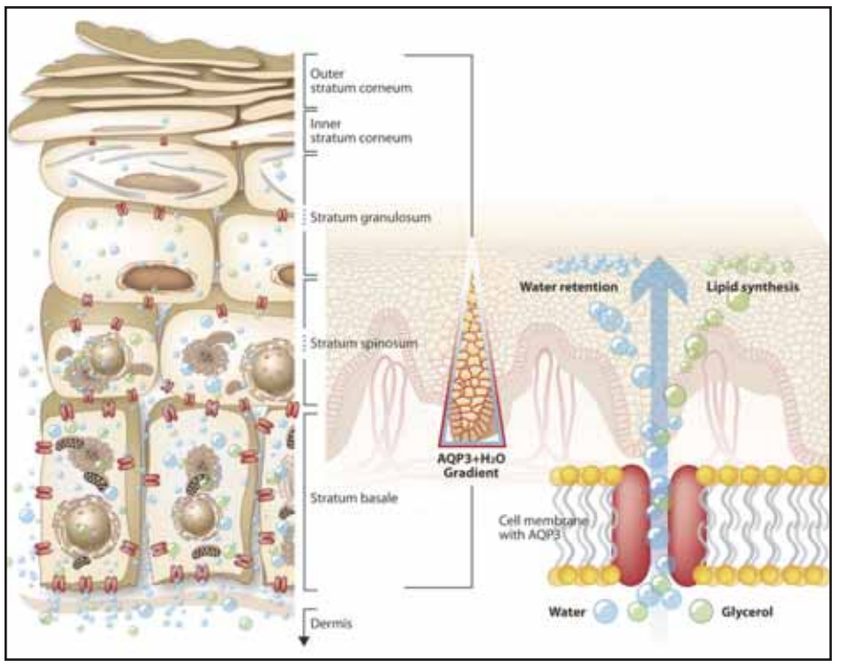

Figure 2. AQP3-mediated mechanism of skin hydration. AQP3 channels in epidermal cell membranes facilitate glycerol and water transport into and between cells. AQP3 is primarily expressed in the stratum basale, with expression decreasing toward the stratum granulosum. This gradient of AQP3 expression corresponds to the decreasing water gradient from the dermis to the stratum corneum. Glycerol in the outer epidermal layers binds and holds water, maintaining optimal skin hydration. In addition, glycerol can increase lipid metabolism, thereby improving SC barrier function.

Clinical Aspects of AQP3

The relationship between the degree of hydration and AQP3 content can help explain various dermatological conditions. The expression of AQP3 channels in human skin is strongly affected by aging and chronic sun exposure, with levels significantly decreased in both, and thus could account for the heightened incidence of skin dryness (xerosis) observed in older people and/or skin areas that have been chronically exposed to sunlight.[3] AQP3 levels have been shown to be decreased in psoriatic lesions.[21] In addition, in psoriatic skin, AQP3 channels were observed in the cytoplasm, rather than being membrane-bound.[21] Since AQP3 must be located in the plasma membrane in order to transport extracellular glycerol and water into cells, this result suggests that AQP3 transport activity is compromised in keratinocytes from psoriatic lesions. It is not surprising, therefore, that AQP3 has been mentioned as a possible factor that could be implicated in a range of skin diseases.[14]

Altering the expression of AQP3 may be a potential mechanism for treating some of these dry skin conditions. The search is currently under way for compounds that can be used to pharmacologically stimulate AQP3 expression, thereby improving the hydration state of the skin by endogenous means. Various agents, primarily from botanical sources, are being investigated that can modulate AQP3 expression, although studies to date have been restricted to *in vitro* or mouse models.[4,22,23]

How water levels are achieved and maintained in the skin has not been a primary focus for dermatologists. Most publications, reports, and commercial communications focus on the maintenance of skin hydration through the use of moisturization products. These products generally contain humectants that bind and hold water in the skin, and lipids to

help prevent water loss, in addition to emollients that impart a soft, smooth feeling to the skin. How water gets into the skin in the first place is probably assumed by most to be related to the general hydration habits of an individual and via unrestricted osmosis. Now, with the discovery of AQPs, we are on our way to understanding how water moves into the viable cells of the epidermis and how this impacts the hydration and integrity of the SC. Evidence of the ability of AQP3 to transport glycerol helps explain previous observations of the prolonged effect of glycerol on skin hydration, referred to as the reservoir effect.[15] The potential exists for AQP3 levels to be manipulated in different ways, thus presenting interesting possibilities for AQP3 modulators to be developed and incorporated into future generations of skin care products.

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